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O-Protected 3-hydroxy-oxazolidin-2,4-diones: novel precursors in the synthesis of α-hydroxyhydroxamic acids

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O-Protected 3-hydroxyoxazolidin-2,4-diones have been prepared in a novel one-pot reaction by subsequent treatment of cyanohydrins with 1,1′-carbonyldiimidazole and *O*-protected hydroxylamines followed by acidic hydrolysis of the intermediate 4-imino-oxazolidin-2-ones. Decarbonylation of *O*-protected 3-hydroxyoxazolidin-2,4-diones by catalytic amounts of sodium methoxide, lithium hydroxide, sodium carbonate and caesium carbonate in methanol afforded *O*-protected α-hydroxyhydroxamic acids in excellent yields. Their deprotection provided a series of novel α-hydroxyhydroxamic acids.

Introduction

α-Hydroxyhydroxamic acids are important derivatives of hydroxamic acids, a class of compounds which displays a broad range of biological activities. Due to the ability of hydroxamic acids to act as chelators for a variety of different metal cations the hydroxamate functionality represents a key pharmacophore in the development of metalloenzyme inhibitors.[1–3]

α-Hydroxyhydroxamates, such as Marimastat and some analogues, have attracted considerable interest in medicinal chemistry as matrix metalloproteinase (MMP) inhibitors.[1,2] Furthermore, *O*-substituted α-hydroxyhydroxamic acids have found wide applications as building blocks for the synthesis of various heterocycles.[4–7]

Due to the diprotic nature of hydroxamic acids, the hydroxamate functionality is often introduced into a molecule in a protected form.[8] In most cases only the hydroxamic acid hydroxy group is protected. Among various protecting groups used in hydroxamic acid chemistry the *O*-benzyl group is one of the most widely used.[9] *O*-Benzylhydroxamates are readily deprotected under mild conditions in high yields by catalytic hydrogenation on Pd–C. Other common protecting groups are for instance *O*-*t*-Bu,[10] *O*-TMS,[11] and *O*-3,4-dimethoxybenzyl (DMB).[12]

Various synthetic methods exist for preparation of hydroxamic acids and their *O*-protected derivatives. Classically, *O*-protected hydroxamic acids are prepared by reacting *O*-protected hydroxylamines with activated carboxylic acids derivatives (*e.g.* acid halides, anhydrides). Because of the importance of the hydroxamic acid functionality a variety of novel methods for the preparation of hydroxamic acids, starting from substituted hydroxylamines and *N*-acyloxyoxazolidinones, *N*-acyl-benzotriazoles or 2-acyloxypyridines, have been developed in recent years.[13–15] Although the methods described above are quite efficient in the preparation of hydroxamic acids the synthesis of α-hydroxyhydroxamic acids and their *O*-protected derivatives is still difficult and yields are often low.

Relatively few synthetic methods exist for the preparation of compounds **7**. Most of the publications relate to coupling reactions of α-hydroxycarboxylic acids with *O*-protected hydroxylamines in the presence of carbodiimides.[16,17] We know of only one article describing a 1,1′-carbonyldiimidazole (CDI) mediated synthesis of an *O*-protected α-hydroxyhydroxamic acid in 18% yield.[18] Just one author refers to a BOP/HOBT coupling procedure for the synthesis of *O*-protected α-hydroxyhydroxamates.[19]

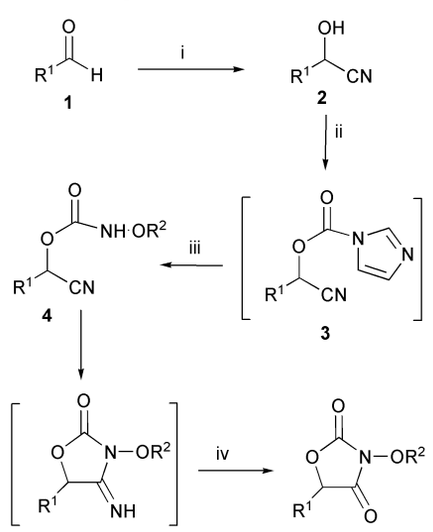
In contrast to the well known synthesis of α-hydroxycarboxamides from 3-alkyl(aryl)-oxazolidin-2,4-diones,[20] the herein described conversion of *O*-substituted 3-hydroxyoxazolidin-2,4-diones (**6**) into **7** has not been reported before. Especially the conversion of a 5,5-disubstituted 3-cyclohexyl-oxazolidin-2,4-dione into the corresponding α-hydroxycarboxamide, reported by Miethchen and Frank, by refluxing the oxazolidin-2,4-dione in methanol in the presence of an excess of sodium methoxide for seven hours attracted our interest.[21]

Results and discussion

Synthesis of *O*-protected 3-hydroxyoxazolidin-2,4-diones (6)

Cyanohydrins (**2**) have been prepared by reactions of aldehydes (**1**) with trimethylsilyl cyanide in almost quantitative yields according to an established literature procedure.[22] Treatment of **2** with CDI in dry dichloromethane at ambient temperature led to imidazolide intermediates **3**, which after addition of *O*-protected hydroxylamines in turn underwent hydroxylaminolysis to the corresponding carbamate intermediates **4**. Ring closure of **4** furnished 4-imino-oxazolidin-2-ones (**5**), which are characterised by two sharp IR-absorptions bands at 1690–1700 cm^{-1} (C=N) and 1790–1805 cm^{-1} (C=O). Subsequent acidic hydrolysis of **5** afforded **6** in overall high yield of 80–92% (Scheme 1).

Compounds **6** have previously been prepared in moderate to good yields by subsequent treatment of α-hydroxy-carboxylic



Scheme 1 *Reagents and Conditions*. i, TMSCN, HCl; ii, CDI; iii, H_2NOR_2; iv, THF, HCl.

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Table 1 Conversion of 5-benzyl-3-benzyloxy-oxazolidin-2,4-dione (**6a**) into *N*-benzyloxy-2-hydroxy-3-phenyl-propionamide (**7a**)

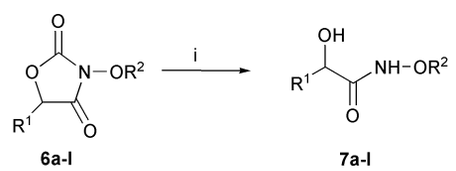
Base[a]	Equivalents	Yield (%)	Time/h
CH_3ONa	4.44	88	1
CH_3ONa	0.44	90	1
CH_3ONa	0.22	92	1
CH_3ONa	0.11	87	1.5
C_2H_5ONa	0.10	80	1
Cs_2CO_3	0.20	66	3
Na_2CO_3	0.20	78	3
LiOH	0.20	80	3

[a] 1 mmol of **6a** was reacted with the appropriate base in 30 mL of methanol.

acid esters with 1,1′-carbonyl-di-(1,2,4-triazole) and hydroxylamines,[23] by carbonylation of *O*-substituted α-hydroxyhydroxamic acids[4] and by reactions of 1,2,5-dioxazian-3,6,-diones with *O*-substituted hydroxylamines.[24]

Decarbonylation of *O*-protected 3-hydroxy-oxazolidin-2,4-diones (6)

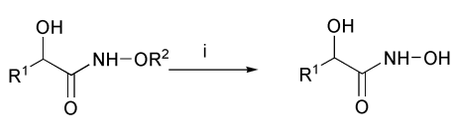
Next we investigated the reactions of **6a** with various bases in methanol (Table 1). Refluxing of **6a** in methanol in the presence of sodium methoxide (0.22 equivalent) for 1 h afforded **7a** in excellent yield of 92% (Scheme 2). When **6a** was treated with sodium ethoxide (0.1 equivalent) under similar conditions **7a** was obtained in somewhat lower yields of 80%. Reactions of **6a** with caesium carbonate, sodium carbonate and lithium hydroxide in methanol at room temperature furnished **7a** in moderate to good yields of 66–80%. Even the treatment of **6a** with an excess of sodium methoxide (4.44 equivalent) provided **7a** in high yield (Table 1).



6a-l **7a-l**

Scheme 2 *Reagents and Conditions*. i, 0.22 equi. NaOMe, MeOH, reflux.

Finally, catalytic hydrogenation of **7d**, **e**, **h**, **i** on Pd–C in methanol provided the novel α-hydroxyhydroxamic acids (**8d**, **e**, **h**, **i**) in high yields of 90–93%. Deprotection of *O*-3,4-dimethoxybenzyl hydroxamate **7j** by DDQ led to **8i** in only 30% yield (Scheme 3). All attempts to synthesise **8i** from **7i** using TFA/DCM were unsuccessful.



7d,e,h,i,j **8d,e,h,i**

Scheme 3 *Reagents and Conditions*. i, H_2, Pd–C, or DDQ.

The structures of the novel compounds were confirmed by IR, ^1H, ^{13}C NMR spectroscopy and elemental analysis.

Conclusions

In conclusion, we have developed a novel and convenient synthetic pathway for the preparation of *O*-protected α-hydroxyhydroxamic acids (**7**), starting from various aldehydes in 66–84% overall yield. Our method includes an operationally simple one pot-synthesis for the preparation of *O*-protected 3-hydroxyoxazolidin-2,4-diones (**6**) and the previously unreported decarbonylation of **6** under mild conditions in the presence of different bases in methanol. Finally, deprotection of **7** led to novel α-hydroxyhydroxamic acids (**8**). We have demonstrated that *O*-protected 3-hydroxyoxazolidin-2,4-diones are valuable precursors in the preparation of *O*-protected α-hydroxyhydroxamic acids. The oxazolidin-2,4-dione ring system serves as protecting group for the alcoholic hydroxyl group and for the hydroxamic acid nitrogen. For medicinal and organic chemists this method offers novel synthetic options in the preparation of α-hydroxyhydroxamic acids (**6**, **7**).

Table 2 Isolated yields of *O*-protected 3-hydroxyoxazolidin-2,4-diones (**6**) and α-hydroxyhydroxamic acids (**7**, **8**)

Entry	R^1	R^2	Yield (%)
6a	$C_6H_5CH_2$	$C_6H_5CH_2$	92
6b	C_6H_5	$C_6H_5CH_2$	85
6c	CH_3	$C_6H_5CH_2$	85
6d	$(CH_3)_2CH$	$C_6H_5CH_2$	90
6e	$(CH_3)_3C$	$C_6H_5CH_2$	85
6f	C_3H_5	$C_6H_5CH_2$	80
6g	C_6H_{11}	$C_6H_5CH_2$	90
6h	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	83
6i	$(C_6H_5)_2CH$	$C_6H_5CH_2$	85
6j	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	80
6k	$(C_6H_5)_2CH$	C_6H_5	81
6l	$(C_6H_5)_2CH$	$(CH_3)_3$	83
7a	$C_6H_5CH_2$	$C_6H_5CH_2$	92
7b	C_6H_5	$C_6H_5CH_2$	89
7c	CH_3	$C_6H_5CH_2$	92
7d	$(CH_3)_2CH$	$C_6H_5CH_2$	89
7e	$(CH_3)_3C$	$C_6H_5CH_2$	88
7f	C_3H_5	$C_6H_5CH_2$	86
7g	C_6H_{11}	$C_6H_5CH_2$	91
7h	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	91
7i	$(C_6H_5)_2CH$	$C_6H_5CH_2$	86
7j	$(C_6H_5)_2CH$	3,4-di-(CH_3O)-$C_6H_3CH_2$	83
7k	$(C_6H_5)_2CH$	C_6H_5	87
7l	$(C_6H_5)_2CH$	$(CH_3)_3$	88
8d	$(CH_3)_2CH$	H	90
8e	C_3H_5	H	91
8h	$C_6H_5CH_2CH_2$	H	92
8i	$(C_6H_5)_2CH$	H	93

Experimental

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 as a solvent. Cyanohydrins (**2**) have been prepared according to an established literature procedure and were used immediately after characterisation by IR spectroscopy.[23]

General procedure for the preparation of 6a–l

A solution of cyanohydrine (6 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyldiimidazole (6.5 mmol) in dry CH_2Cl_2 (6 mL) under ice cooling. After stirring at room temperature for 10 min, the appropriate hydroxylamine (6 mmol) was added and the reaction mixture was stirred at room temperature for 45–60 min. The solvent was removed under reduced pressure and the residue was dissolved in THF (3 mL). Hydrochloric acid (10 mL, 20%) was added under ice cooling and the mixture was stirred again for 30 min. The reaction mixture was extracted twice with EtOAc and the combined extracts were dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded oily residues, which were crystallised from EtOAc–hexane to give **6a**–**l** as colourless solids. Table 2 summarises the isolated yields of **6**, **7** and **8**.

5-Benzyl-3-benzyloxy-oxazolidin-2,4-dione, 6a

(1.65 g, 92%) as colourless solid, mp 139 °C (from EtOAc–hexane). (Found: C, 68.43; H, 5.08; N, 4.90. $C_{17}H_{15}NO_4$ requires C, 68.68; H, 5.09; N, 4.71%); ν_{max}(KBr)/cm^{-1} 1827, 1751; δ_H(DMSO-d_6) 3.11–3.27 (m, 2H), 4.85 (q, J = 10.43 Hz, 2H), 5.35 (q, J = 4.58 Hz, 1H), 7.22–7.41 (m, 10H); δ_C(DMSO-d_6) 35.83, 78.37, 79.27, 127.63, 128.82, 128.89, 129.66, 129.97, 130.01, 133.63, 134.39, 151.38, 166.91.

3-Benzyloxy-5-phenyl-oxazolidin-2,4-dione, 6b

(1.45 g, 85%) as colourless solid, mp 90 °C (from EtOAc–hexane). (Found: C, 67.78; H, 4.60; N, 5.09. $C_{16}H_{13}NO_4$ requires C, 67.84; H, 4.63; N, 4.94%); ν_{max}(KBr)/cm^{-1} 1817, 1751; δ_H(DMSO-d_6) 4.96 (q, J = 10.43 Hz, 2H), 5.46 (s, 1H), 7.35–7.48 (m, 10H); δ_C(DMSO-d_6) 78.37, 79.27, 127.63, 128.82, 128.89, 129.66, 129.97, 130.01, 133.63, 134.39, 151.38, 166.91.

3-Benzyloxy-5-methyl-oxazolidin-2,4-dione, 6c

(1.13 g, 85%) as colourless solid, mp 69 °C (from EtOAc–hexane). (Found: C, 59.81; H, 5.15; N, 6.20. $C_{11}H_{11}NO_4$ requires C, 59.73; H, 5.01; N, 6.33%); ν_{max}(KBr)/cm^{-1} 1825, 1750; δ_H(DMSO-d_6) 1.44 (d, J = 6.87 Hz, 3H), 5.10 (q, J = 7.12 Hz, 1H), 5.14 (q, J = 10.43 Hz, 2H), 7.40–7.50 (m, 5H); δ_C(DMSO-d_6) 16.05, 75.05, 79.14, 128.87, 129.65, 130.13, 133.82, 151.58, 168.38.

3-Benzyloxy-5-isopropyl-oxazolidin-2,4-dione, 6d

(1.34 g, 90%) as colourless solid, mp 60 °C (from EtOAc–hexane). (Found: C, 62.64; H, 6.07; N, 5.62. $C_{13}H_{15}NO_4$ requires C, 62.75; H, 6.15; N, 5.53%); ν_{max}(KBr)/cm^{-1} 1825, 1750; δ_H(DMSO-d_6) 0.80 (d, J = 6.85 Hz, 3H), 0.82 (d, J = 6.85 Hz, 3H), 1.85–1.95 (m, 1H), 4.55 (d, J = 8.91 Hz, 1H), 4.82 (s, 2H), 7.30–7.41 (m, 5H); δ_C(DMSO-d_6) 17.01, 19.10, 31.70, 76.80, 79.45, 126.61, 127.38, 127.85, 131.55, 151.38, 166.91.

3-Benzyloxy-5-*tert*-butyl-oxazolidin-2,4-dione, 6e

(1.35 g, 85%) as colourless solid, mp 64 °C (from EtOAc–hexane). (Found: C, 63.73; H, 6.58; N, 5.53. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%); ν_{max}(KBr)/cm^{-1} 1820, 1750; δ_H(DMSO-d_6) 0.92 (s, 9H), 4.73 (s, 1H), 5.13 (s, 2H), 7.40–7.49 (m, 5H); δ_C(DMSO-d_6) 24.58, 34.46, 79.01, 84.60, 128.82, 129.66, 130.10, 133.77, 151.61, 166.48.

3-Benzyloxy-5-cyclopropyl-oxazolidin-2,4-dione, 6f

(1.18 g, 80%) as colourless solid, mp 89 °C (from EtOAc–hexane). (Found: C, 63.01; H, 5.34; N, 5.54. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.66%); ν_{max}(KBr)/cm^{-1} 1825, 1753; δ_H(DMSO-d_6) 0.41–0.68 (m, 4H), 1.17–1.26 (m, 1H), 4.55 (d, J = 8.90 Hz, 1H), 5.13 (q, J = 10.43 Hz, 2H), 7.41–7.60 (m, 5H); δ_C(DMSO-d_6) 8.87, 27.60, 76.83, 79.46, 126.61, 127.38, 127.85, 131.55, 149.27, 164.55.

3-Benzyloxy-5-cyclohexyl-oxazolidin-2,4-dione, 6g

(1.56 g, 90%) as colourless solid, mp 77 °C (from EtOAc–hexane). (Found: C, 66.60; H, 6.64; N, 4.91. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); ν_{max}(KBr)/cm^{-1} 1817, 1757; δ_H(DMSO-d_6) 0.94–1.34 (m, 6H), 1.68–1.85 (m, 5H), 4.87 (d, J = 4.58 Hz, 1H), 5.14 (q, J = 10.43 Hz, 2H), 7.40–7.48 (m, 5H); δ_C(DMSO-d_6) 25.30, 25.45, 25.69, 25.83, 27.41, 38.69, 78.98, 81.69, 128.81, 129.65, 130.18, 133.73, 151.80, 166.86.

3-Benzyloxy-5-phenethyl-oxazolidin-2,4-dione, 6h

(1.55 g, 83%) as colourless solid, mp 120 °C (from EtOAc–hexane). (Found: C, 69.40; H, 5.58; N, 4.45. $C_{18}H_{17}NO_4$ requires C, 69.44; H, 5.50; N, 4.50%); ν_{max}(KBr)/cm^{-1} 1830, 1750; δ_H(DMSO-d_6) 1.82–2.10 (m, 2H), 2.60 (t, J = 8.14 Hz, 2H), 4.85 (q, J = 10.43 Hz, 2H), 4.90 (q, J = 7.63 Hz, 1H), 7.21–7.41 (m, 10H); δ_C(DMSO-d_6) 30.48, 33.47, 77.32, 79.30, 126.45, 128.65, 128.79, 129.60, 129.95, 130.01, 133.63, 134.40, 151.35, 166.85.

5-Benzhydryl-3-benzyloxy-oxazolidin-2,4-dione, 6i

(1.79 g, 80%) as colourless solid, mp 125 °C (from EtOAc–hexane). (Found C, 73.98; H, 5.13; N, 3.75. $C_{23}H_{19}NO_4$ requires C, 73.78; H, 5.00; N, 3.80%); ν_{max}(KBr)/cm^{-1} 1825, 1755; δ_H(DMSO-d_6) 4.67 (q, J = 10.18 Hz, 2H), 4.75 (d, J = 4.57 Hz, 1H), 5.92(d, J = 4.58Hz, 1H), 7.21–7.40 (m, 15H); δ_C(DMSO-d_6) 74.16, 79.31, 79.80, 126.59, 127.45, 128.56, 128.93, 129.45, 129.96, 137.91, 141.59, 150.81, 166.26.

5-Benzyhydryl-3-(3,4-dimethoxy-benzyloxy)-oxazolidin-2,4-dione, 6j

(2.08 g, 80%) as colourless solid, mp 118 °C (from EtOAc–hexane). (Found: C, 69.19; H, 5.39; N, 3.31. $C_{25}H_{23}NO_6$ requires C, 69.27; H, 5.35; N, 3.23%); ν_{max}(KBr)/cm^{-1} 1825, 1750; δ_H(DMSO-d_6) 3.74 (s, 3H), 3.76 (s, 3H), 4.62 (q, J = 9.92 Hz, 2H), 4.68 (d, J = 4.58 Hz, 1H), 5.93 (d, J = 4.58 Hz, 1H), 6.82–6.97 (m, 3H), 7.25–7.80 (m, 10H); δ_C(DMSO-d_6) 51.10, 55.81, 55.80, 79.31, 79.69, 111.72, 113.53, 123.02, 125.64, 127.47, 127.88, 128.59, 128.91, 129.36, 137.97, 139.53, 148.89, 150.04, 151.28, 166.29.

5-Benzhydryl-3-phenoxy-oxazolidine-2,4-dione, 6k

(1.75 g, 81%) as colourless solid, mp 153 °C (from EtOAc–hexane). (Found: C, 73.50; H, 4.81; N, 4.01. $C_{22}H_{17}NO_4$ requires C, 73.53; H, 4.77; N, 3.90%); ν_{max}(KBr)/cm^{-1} 1830, 1755; δ_H(DMSO-d_6) 4.82 (d, J = 4.57 Hz, 1H), 6.04 (d, J = 4.58 Hz, 1H), 7.16–7.44 (m, 15H); δ_C(DMSO-d_6) 52.49, 74.46, 112.61, 113.14, 120.91, 122.62, 126.95, 127.55, 128.82, 129.35, 129.67, 129.88, 130.28, 140.76, 153.98, 159.90.

5-Benzhydryl-3-*tert*-butoxy-oxazolidine-2,4-dione, 6l

(1.69 g, 83%) as colourless solid, mp 115 °C (from EtOAc–hexane). (Found: C, 70.78; H, 6.24; N, 4.13. $C_{20}H_{21}NO_4$ requires C, 70.60; H, 6.08; N, 4.01%); ν_{max}(KBr)/cm^{-1} 1820, 1745; δ_H(DMSO-d_6) 1.15 (s, 9H), 4.70 (d, J = 4.57 Hz, 1H), 5.90 (d, J = 4.58 Hz, 1H), 7.20–7.42 (m, 10H); δ_C(DMSO-d_6) 26.68, 52.49, 55.75, 79.80, 111.67, 112.85, 121.79, 126.44, 128.49, 129.35, 141.98, 142.30, 150.93, 166.73.

Synthetic procedures for preparation of 7a–l

A: General procedure; using sodium methoxide. To a stirred solution of **6a–l** (1 mmol) in methanol (30 mL) was added NaOMe (0.22 mmol) and the reaction mixture was refluxed for 1 h. The reaction mixture was concentrated *in vacuo*, water (15 mL) was added and the mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Recrystallisation of the remaining solids from EtOAc–hexane provided **7a–l** as colourless solids.

B: Synthesis of 7a using sodium ethoxide. To a stirred solution of **6a** (1 mmol) in methanol (30 ml) was added NaOEt (0.1 mmol) and the mixture was refluxed for 1 h. The solvent was evaporated, water (15 mL) was added and the mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Recrystallisation of the remaining solid from EtOAc–hexane provided **7a** as a colourless solid.

C: Synthesis of 7a using caesium carbonate, sodium carbonate and lithium hydroxide. To a stirred solution of **6a** (1 mmol) in methanol (30 mL) was added the appropriate base (0.2 mmol)

and the reaction mixture was kept at room temperature for 3 h. After neutralization with aqueous citric acid (5%) the reaction mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **7a** as a solid product, which was recrystallised from EtOAc–hexane.

_N_-Benzyloxy-2-hydroxy-3-phenyl-propionamide, 7a

(0.25 g, 92%) as colourless solid, mp 135 °C (from EtOAc–hexane). (Found: C, 70.67; H, 6.31; N, 5.23. $C_{16}H_{17}NO_3$ requires C, 70.83; H, 6.32; N, 5.16%); ν_{max}(KBr)/cm^{-1} 1668; δ_H(DMSO-d_6) 2.74–2.95 (m, 2H), 4.10 (m, 1H), 4.71 (s, 2H), 5.50 (d, J = 6.36 Hz, 1H), 7.17–7.35 (m, 10H), 11.06 (s, 1H); δ_c(DMSO-d_6) 40.72, 71.55, 77.14, 126.44, 128.33, 128.55, 128.60, 129.16, 129.84, 136.25, 138.42, 170.16.

_N_-Benzyloxy-2-hydroxy-2-phenylacetamide, 7b

(0.23 g, 89%) as colourless solid, mp 107 °C (from EtOAc–hexane). (Found: C, 70.19; H, 6.01; N, 5.23. $C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88; N, 5.44%); ν_{max}(KBr)/cm^{-1} 1672; δ_H(DMSO-d_6) 4.91 (d, J = 2.29 Hz, 1H), 5.45 (s, 2H), 5.92 (d, J = 3.31 Hz, 1H), 7.24–7.40 (m, 10H), 11.06 (s, 1H); δ_C(DMSO-d_6) 75.66, 77.14, 126.40, 128.35, 128.59, 128.66, 129.23, 129.89, 136.40, 138.49, 170.16.

_N_-Benzyloxy-2-hydroxy-propionamide, 7c

(0.18 g, 92%) as colourless solid, mp 59 °C (from EtOAc–hexane). (Found: C, 61.44; H, 6.66; N, 7.23. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.71; N, 7.17%); ν_{max}(KBr)/cm^{-1} 1664; δ_H (DMSO-d_6) 1.20 (d, J = 6.87 Hz, 3H), 3.97 (m, 1H), 4.79 (s, 2H), 5.36 (d, J = 5.34 Hz, 1H), 7.32–7.42 (m, 5H), 11.01 (s, 1H); δ_C(DMSO-d_6) 21.32, 66.75, 77.07, 128.54, 128.60, 129.08, 136.29, 171.51.

_N_-Benzyloxy-2-hydroxy-3-methyl-butyramide, 7d

(0,20 g, 89%) as colourless solid, mp 69 °C (from EtOAc–hexane). (Found: C, 64.60; H, 7.75; N, 6.11. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27%); ν_{max}(KBr)/cm^{-1} 1670; δ_H (DMSO-d_6) 0.80 (d, J = 6.87 Hz, 3H), 0.85 (d, J = 6.87 Hz, 3H), 1.87–1.95 (m, 1H), 3.60 (t, J = 5.85 Hz, 1H), 4.80 (s, 2H), 5.26 (d, J = 6.11 Hz, 1H), 7.31–7.42 (m, 5H), 11.00 (s, 1H); δ_C(DMSO-d_6) 17.07, 19.15, 31.75, 75.12, 77.11, 128.51, 128.58, 129.01, 136.37, 170.35.

_N_-Benzyloxy-2-hydroxy-3,3-dimethyl-butyramide, 7e

(0.21g, 88%) as colourless solid, mp 54 °C (from EtOAc–hexane); (Found: C, 66.01; H, 8.19; N, 6.08$C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); ν_{max}(KBr)/cm^{-1} 1668; δ_H(DMSO-d_6) 0.86 (s, 9H), 3.43 (d, J = 5.85 Hz, 1H), 4.79 (s, 2H), 5.24–5.28 (m, 1H), 7.31–7.42 (m, 5H), 10.92 (s, 1H); δ_C(DMSO-d_6) 26.38, 34.79, 77.07, 77.60, 127.74, 128.57, 128.96, 136.44, 169.96.

_N_-Benzyloxy-2-cyclopropyl-2-hydroxy-acetamide, 7f

(0.19 g, 86%) as colourless solid, mp 110 °C (from EtOAc–hexane). (Found: C, 65.00; H, 6.75; N, 6.20. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%); ν_{max}(KBr)/cm^{-1} 1665; δ_H(DMSO-d_6) 0.43–.69 (m, 4H), 1.19–1.29 (m, 1H), 4.65 (d, J = 8.90 Hz, 1H), 4.98 (s, 2H), 5.21 (d, J = 6.00 Hz, 1H), 7.41–7.60 (m, 5H), 11.00 (s, 1H); δ_C(DMSO-d_6) 8.85, 27.90, 76.81, 79.47, 126.60, 127.37, 127.82, 131.55, 169.54.

_N_-Benzyloxy-2-cyclohexyl-2-hydroxy-acetamide, 7g

(0.24 g, 91%) as colourless solid, mp 112 °C (from EtOAc–hexane). (Found: C, 68.55; H, 7.90; N, 5.58. $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32%); ν_{max}(KBr)/cm^{-1} 1672; δ_H(DMSO-d_6) 1.00–1.24 (m, 5H), 1.45–1.72 (m, 6H), 3.58 (t, J = 5.34 Hz, 1H), 4.79 (s, 2H), 5.21 (d, J = 6.10 Hz, 1H), 7.33–7.41 (m, 5H), 10.97 (s, 1H); δ_C(DMSO-d_6) 25.94, 26.11, 26.28, 27.09, 29.03, 41.51, 74.66, 77.10, 128.50, 128.56, 129.04, 136.35, 170.23.

_N_-Benzyloxy-2-hydroxy-4-phenyl-butyramide, 7h

(0.26 g, 91%) as colourless solid, mp 98 °C (from EtOAc–hexane). (Found: C, 71.28; H, 6.88; N, 5.12. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91%); ν_{max}(KBr)/cm^{-1} 1645; δ_H(DMSO-d_6) 1.72–1.91 (m, 2H), 2.60 (t, J = 7.63 Hz, 2H), 3.90 (m, 1H), 4.80 (s, 2H), 5.48 (d, J = 5.85 Hz, 1H), 7.15–7.42 (m, 10H), 11.09 (s, 1H); δ_C(DMSO-d_6) 30.97, 36.54, 69.91, 77.08, 126.08, 128.52, 128.58, 128.66, 129.05, 136.34, 142.05, 170.80.

_N_-Benzyloxy-2-hydroxy-3,3-diphenylpropionamide, 7i

(0.30 g, 86%) as colourless solid, mp 130 °C (from EtOAc–hexane). (Found: C, 76.16; H, 6.15; N, 4,14. $C_{22}H_{21}NO_3$ requires C, 76.06; H, 6.09; N, 4.33%); ν_{max}(KBr)/cm^{-1} 1672; δ_H(DMSO-d_6) 4.34 (d, J = 10.43 Hz, 1H), 4.40 (q, J = 10.18 Hz, 2H), 4.65 (t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.10–7.37 (m, 15H), 11.09 (s, 1H); δ_C(DMSO-d_6) 55.76, 72.73, 77.07, 111.67, 112.85, 121.79, 126.44, 128.34, 128.49, 128.93, 129.35, 141.98, 142.30, 148.85, 149.21, 169.08.

***N*-(3,4-Dimethoxy-benzyloxy)-2-hydroxy-3,3-diphenyl-propionamide, 7j**

(0.34 g, 83%) as colourless solid, mp °C (from EtOAc–hexane). (Found C, 70.82; H, 6.30; N, 3,34. $C_{24}H_{25}NO_5$ requires C, 70.75; H, 6.18; N, 3.44%); ν_{max}(KBr)/cm^{-1} 1670; δ_H(DMSO-d_6) 3.74 (s, 6H), 4.30 (d, J = 10.43 Hz, 1H), 4.36 (q, J = 10.18 Hz, 2H), 4.62 (t, J = 7.37 Hz, 1H), 5.71 (d, J = 7.12 Hz, 1H), 6.70–6.89 (m, 3H), 7.14–7.35 (m, 10H), 11.09 (s, 1H); δ_C(DMSO-d_6) 54.34, 55.76, 72.73, 77.07, 111.67, 112.85, 121.79, 126.44, 126.63, 128.34, 128.49, 128.93, 129.35, 141.98, 142.30, 148.85, 149.21, 169.08.

2-Hydroxy-_N_-phenoxy-3,3-diphenyl-propionamide, 7k

(0.29 g, 87%) as colourless solid, mp 125 °C (from EtOAc–hexane). (Found: C, 75.66; H, 5.74; N, 4.20. $C_{21}H_{19}NO_3$ requires C, 75.45; H, 5.74; N, 4.31%); ν_{max}(KBr)/cm^{-1} 1670; δ_H(DMSO-d_6) 4.34 (d, J = 10.43 Hz, 1H), 4.65 (t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.07–7.40 (m, 15H), 11.01 (s, 1H); δ_C(DMSO-d_6) 55.76, 72.73, 112.61, 113.14, 120.91, 122.62, 126.95, 127.55, 128.82, 129.35, 129.67, 129.88, 130.28, 140.76, 169.08.

N-*tert*-Butoxy-2-hydroxy-3,3-diphenyl-propionamide, 7l

(0.27g, 88%) as colourless solid, mp 115 °C (from EtOAc–hexane). (Found: C, 72.82; H, 7.40; N, 4.47. $C_{19}H_{23}NO_3$ requires C, 72.65; H, 7.28; N, 4.47%); ν_{max}(KBr)/cm^{-1} 1668; δ_H(DMSO-d_6) 1.18 (s, 9H), 4.35 (d, J = 10.43 Hz, 1H), 4.66 (t, J = 7.36 Hz, 1H), 5.80 (d, J = 7.13 Hz, 1H), 7.08–7.38 (m, 10H), 11.08 (s, 1H); δ_C(DMSO-d_6) 26.70, 52.50, 55.76, 79.73, 111.68, 112.84, 121.79, 126.44, 128.49, 129.35, 141.98, 142.32, 169.01.

General procedure for the preparation of 8d, e, h, i

7d, **e**, **h**, **i**, were hydrogenated in MeOH using catalytic amounts of 10% Pd/C for 3 h. The suspension was filtered and the solvent was evaporated to give **8d**, **e**, **h**, **i** as colourless solids.

2,_N_-Dihydroxy-3-methyl-butyramide, 8d

(0.12 g, 90%), as colourless solid, mp 87 °C. (Found: C, 45.32; H, 8.45; N, 10.65. $C_5H_{11}NO_3$ requires C, 45.10; H, 8.33; N, 10.52%); ν_{max}(KBr)/cm^{-1} 1670; δ_H(DMSO-d_6) 0.80 (d, J =

6.87 Hz, 3H), 0.87(d, J = 6.87 Hz, 3H), 1.88–1.97 (m, 1H), 3.63 (t, J = 5.86 Hz, 1H), 5.30 (d, J = 6.11 Hz, 1H), 8.71 (s, 1H), 10.50 (s, 1H); δ_C(DMSO-d_6) 17.18, 19.25, 31.80, 75.20, 170.50.

2,*N*-Dihydroxy-3,3-dimethyl-butyramide, 8e

(0.13 g, 91%) as colourless solid; mp 93 °C. (Found: C, 49.15; H, 9.10; N, 9.40. $C_6H_{13}NO_3$ requires C, 48.97; H, 8.90; N, 9.52%); ν_{max}(KBr)/cm^{-1} 1667; δ_H(DMSO-d_6) 0.9 (s, 9H), 3.50 (d, J = 5.85 Hz, 1H), 5.28 (m, 1H), 8.75 (s, 1H), 10.92 (s, 1H); δ_C(DMSO-d_6) 26.38, 34.80, 77.10, 170.10.

2,*N*-Dihydroxy-4-phenyl-butyramide, 8h

(0.18 g, 92%) as colourless solid, mp 145 °C. (Found: C, 61.65; H, 6.83; N, 7.01. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.71; N, 7.17%); ν_{max}(KBr)/cm^{-1} 1640; δ_H(DMSO-d_6) 1.71–1.93 (m, 2H), 2.67–2.68 (m, 2H), 3.81–3.86 (m, 1H), 5.40 (d, J = 5.85 Hz, 1H), 7.15–7.80 (m, 5H), 8.71 (s, 1H), 10.47 (s, 1H); δ_C(DMSO-d_6) 31.14, 36.65, 69.82, 126.07, 128.65, 128.67, 142.14, 170.55.

2,*N*-Dihydroxy-3,3-diphenyl-propionamide, 8i

(0.24 g, 93%) as colourless solid, mp 175 °C. (Found: C, 70.15; H, 6.01; N, 5.65. $C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88; N, 5.44); ν_{max}(KBr)/cm^{-1} 1672; δ_H(DMSO-d_6) 4.43 (d, J = 10.43 Hz, 1H), 4.70 (t, J = 7.37 Hz, 1H), 5.79 (d, J = 7.12 Hz, 1H), 7.16–7.30 (m, 10H), 8.75 (s, 1H), 10.53 (s, 1H); δ_C(DMSO-d_6) 55.80, 72.81, 111.67, 112.85, 121.79, 126.44, 128.49, 129.35, 141.98, 142.30, 170.10.

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